

Effects of Exercise Intervention in Subjects with Metabolic Dysfunction–Associated Steatotic Liver Disease

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent liver disorder globally, including in Asia-Pacific countries. In addition to contributing to severe liver disorders, MASLD increases the risk of various complications. Currently, resmetirom is the only U.S. Food and Drug Administration-approved treatment for MASLD-related fibrosis in the United States. Therefore, lifestyle modifications, particularly regular exercise, remain a crucial approach in managing MASLD. Exercise is generally classified into two types: aerobic and resistance. The two forms offer benefits for individuals with MASLD, despite the difference between their effects and underlying mechanisms. Aerobic exercise is accessible, low cost, and promotes high energy expenditure, improving several MASLD-related clinical parameters. However, associated fatigue and discomfort can reduce long-term adherence. Resistance exercise, referring to muscle contractions performed to counteract external resistance, enhances muscle strength, muscle mass, and bone mineral density while also helping to correct metabolic derangement. It is especially suitable for subjects with MASLD who cannot conduct aerobic exercise or have poor cardiorespiratory function. Mechanistically, aerobic exercise enhances insulin sensitivity, while resistance exercise improves metabolic flexibility through adenosine monophosphate-activated protein kinase activation, muscle fiber adaptation, and muscle-liver cross-talk. In terms of aerobic training, traditional moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) have shown comparable benefits. This review is designed to offer refreshed perspectives on the advantages of exercise, compare the effects and mechanisms of aerobic and resistance exercise, and evaluate the advantages and disadvantages of MICT and HIIT, with emphasis on their impact on hepatic steatosis in subjects with MASLD.

Key words: Non-alcoholic fatty liver disease, Metabolic syndrome, Exercise, Insulin resistance

INTRODUCTION

Fatty liver disease, also known as steatotic liver disease, is a common liver disease globally.¹⁻³ The presence of fatty liver is an essential criterion for metabolic dysfunction-associated fatty liver disease or metabolic dysfunction-associated steatotic liver disease (MASLD), both of which align with the traditional term non-alcoholic fatty liver disease.^{2,3} To diagnose MASLD, apart from hepatic steatosis,

at least one of five cardiometabolic risk factors—body mass index (BMI), waist circumference, glycemic profile, blood pressure, hypertriglyceridemia, or low serum high-density lipoprotein cholesterol—must be present.³ Liver steatosis can be confirmed through biopsy or imaging, ensuring that excessive alcohol consumption is ruled out as a causative factor.

In this review, MASLD is recognized as a risk factor for both hepatic and extra-hepatic complications, including diabetes mellitus

Received March 10, 2025
Reviewed March 27, 2025
Accepted June 4, 2025

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and obesity.³ Currently, resmetirom is the only approved treatment for MASLD-related significant liver fibrosis in the United States.⁴ Therefore, lifestyle modifications, particularly exercise, remain a key strategy for managing MASLD.^{5,6}

Exercise has demonstrated benefits for subjects with various health conditions, including MASLD,⁵⁻¹⁹ by enhancing energy consumption and muscle strength.^{5,6} Exercise can be generally categorized into aerobic and resistance types, both of which improve metabolic disorders in MASLD patients,^{6,9,12} despite the difference in their clinical effects and underlying mechanisms. Aerobic exercise primarily enhances insulin sensitivity, while resistance exercise improves metabolic flexibility through adenosine monophosphate-activated protein kinase (AMPK) activation, muscle fiber adaptation, and muscle-liver cross-talk.¹¹ Reviews regarding benefits of exercise for subjects with MASLD have been published.^{5,6,11-19} The impacts of frequency, intensity, and duration of exercise protocols have been explored previously.¹² This review aims to update and compare the outcomes of various aerobic and resistance exercise programs in MASLD patients, focusing on the effects of liver fat reduction. Additionally, the potential mechanisms accounting for the improve-

ment of hepatic steatosis in each exercise type will be discussed. Furthermore, within aerobic exercise, the review will introduce the features and benefits of moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT).

IMPORTANCE OF LIFESTYLE INTERVENTIONS

MASLD is the liver manifestation of metabolic syndrome, and lifestyle interventions such as weight loss, energy restriction, and exercise are fundamental to its treatment (Fig. 1). Currently, there are no approved pharmacological interventions in most parts of the world. Therefore, lifestyle modifications remain crucial for liver fat reduction and prevention of liver disease progression.^{20,21} Additionally, these interventions provide benefits beyond the liver, helping to manage extra-hepatic complications like obesity and diabetes mellitus.^{22,23}

Weight loss

Weight loss can be achieved through various strategies and even

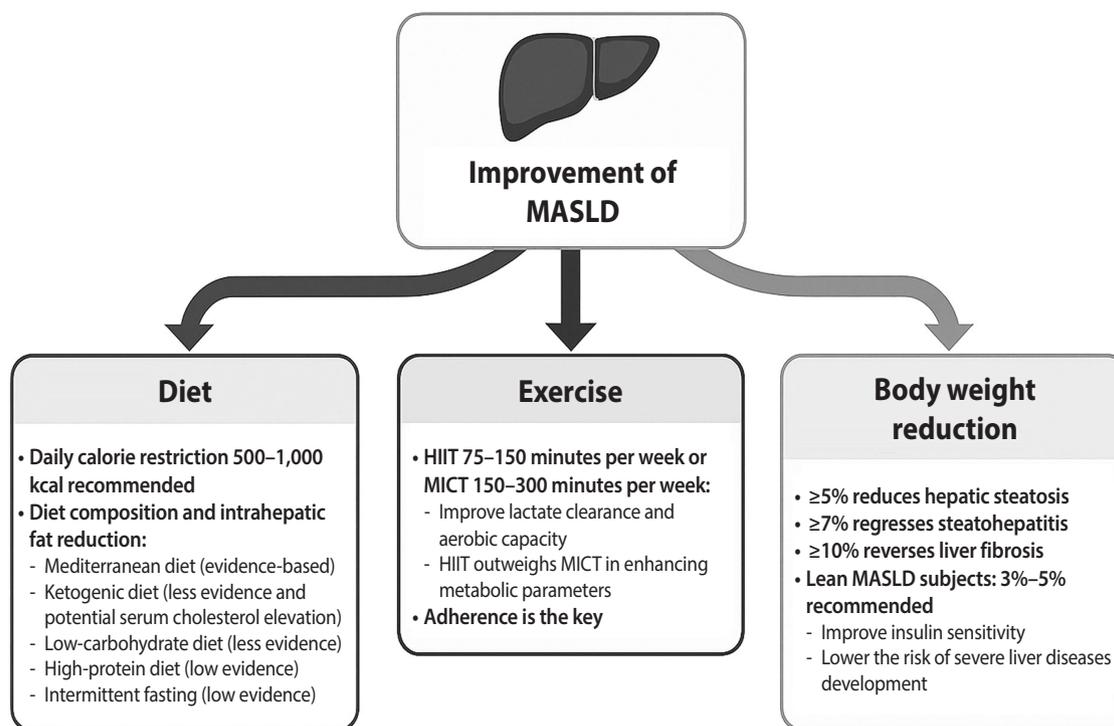


Figure 1. Features and recommendations of lifestyle changes in subjects with metabolic dysfunction-associated steatotic liver disease (MASLD).²⁵⁻²⁷ HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.

pharmaceutical intervention. It has been shown to reduce liver fat; improve glucose control and insulin sensitivity; and lower the risk of type 2 diabetes mellitus, cardiovascular diseases (CVDs), and severe liver diseases.²⁴⁻²⁷ According to the American Gastroenterological Association guidelines, a body weight reduction of at least 5% can reduce hepatic steatosis, 7% or more can regress steatohepatitis, and a 10% or greater reduction can reverse liver fibrosis.²⁵ For lean MASLD subjects (not overweight or obese), a weight reduction of 3% to 5% is recommended.^{24,25}

Diet

Dietary strategies for managing MASLD include restriction of calorie intake, selection of appropriate diet patterns, and optimization of meal timing and interval. Calorie restriction is essential in MASLD improvement, with a recommended daily reduction of 500 to 1,000 kcal. Ideally, total daily calorie intake should be limited to around 1,200 kcal for female subjects and 1,400 to 1,500 kcal for male subjects. Diet control supports weight loss, improves insulin resistance, and reduces liver fat.^{25,26} Notably, the effect of intrahepatic fat reduction can persist even if some weight is regained.²⁷

Other than energy restriction, diet composition plays a crucial role in health outcomes and the level of intrahepatic fat. Low-carbohydrate diets and the Mediterranean diet (MD) are particularly beneficial.^{26,28} The MD consists of nutrient-rich foods such as fruits, vegetables, olive oil, nuts, seeds, legumes, minimally processed whole grains, and omega-3 fatty acid-rich fish.²⁸ Considering the nature of fat, dairy products, red meat, and processed meats should be limited. Both the American College of Cardiology and the American Heart Association recommend the MD for subjects at risk of CVD, as well as those with MASLD. Additionally, previous studies indicated that the MD is associated with a lower risk of hepatocellular carcinoma in MASLD patients.²⁹

Along with MD, the ketogenic diet (KD) has also been recommended for improving MASLD.²⁶ The KD is characterized by low proportions of proteins and carbohydrates, with a relatively high-fat content. Reducing carbohydrate intake plays a key role in MASLD improvement. Through modification of mitochondrial function and hepatic oxidation status, ketone body production is enhanced. While intrahepatic triglyceride synthesis remains unaf-

ected, visceral fat is reduced with KD consumption.³⁰ Although KD offers potential benefits for MASLD patients, animal and clinical studies have highlighted certain risks associated with its use. Therefore, the safety of KD application in subjects with MASLD is uncertain.³¹

Recently, alternative dietary approaches, such as high-protein diets and intermittent fasting, have been introduced for subjects with CVD and MASLD.²⁶ High-protein diets have been shown to markedly decrease serum inflammatory biomarkers,³² while sugar-restricted diets have demonstrated a reduction in intrahepatic fat in adolescents with MASLD.³³ However, clinical trials on these emerging dietary interventions are limited, and their effectiveness and safety have yet to be fully established. Further research is needed to confirm their long-term benefits for MASLD management.

Exercise

Exercise is a useful way for correcting metabolic derangements by improving glucose and lipid metabolism.³⁴⁻³⁶ It enhances peripheral insulin sensitivity, reduces liver lipogenesis, facilitates adipose tissue lipolysis, and ultimately reduces liver fat, resulting in improvement of MASLD. Exercise can be classified into aerobic and resistance types,^{35,36} which will be discussed in detail in the following sections.

The benefit of a low-calorie diet through body weight reduction can be amplified when combined with exercise. For instance, pairing exercise with the MD can decrease body weight, visceral adipose tissue, and liver fat more effectively than the MD without it.³⁴⁻³⁶

Other behavioral modifications

In addition to weight loss, diet control, and exercise, lifestyle interventions for subjects with MASLD should include avoidance of harmful habits such as drinking and cigarette smoking, as these behaviors potentially accelerate liver disease progression.³⁷ Studies have demonstrated that even light-to-moderate consumption of alcohol is associated with accumulation of liver fat and the advancement of hepatic fibrosis. Synergistically, in the presence of obesity, the risk of various liver diseases is heightened.³⁸ Therefore, counseling and educational programs are recommended to help MASLD patients reduce these risky behaviors and lower their risk of progressing to liver fibrosis.³⁹

Table 1. Comparison of aerobic vs. resistance exercise in subjects with metabolic dysfunction-associated steatotic liver disease¹²

| | Aerobic exercise | Resistance exercise |
|-------------------------------|--|---|
| Metabolic parameters | Improved | Improved |
| Features | High energy consumption and reduction of body weight | Lower intensity and energy consumption than aerobic exercise |
| Reduction of intrahepatic fat | Yes | Yes, but might be independent of body weight loss. |
| Mechanisms of improvement | Improve insulin sensitivity | Improve metabolic flexibility through AMPK activation, muscle fiber adaptation, and muscle-liver cross-talk. Improve lipid metabolism in the liver. |
| Advantages | Convenient, low cost, and widely available | Feasible for subjects with cardiorespiratory disorders or who cannot tolerate intensive exercise |
| Disadvantages | Fatigue sensation and physiological discomfort lead to decreased adherence | High cost and individualized equipment might be required. |

AMPK, adenosine monophosphate-activated protein kinase.

CLINICAL EVIDENCE OF EXERCISE INTERVENTION

Both aerobic and resistance exercises improve liver disease outcomes and extra-hepatic comorbidities in individuals with MASLD (Table 1). However, the clinical characteristics and underlying mechanisms of improvement differ between the two exercise types.

Aerobic exercises like jogging and swimming offer several advantages, including convenience, low cost, and easy accessibility.³⁴⁻³⁶ They typically result in high energy consumption, favorable reduction of body weight, and improvement of metabolic variables associated with MASLD.^{35,36} However, several disadvantages exist, including fatigue and physical discomfort, which can diminish long-term compliance in some subjects. Furthermore, moderate to intense aerobic activities require a certain level of cardiorespiratory and mobility fitness. For subjects with underlying cardiorespiratory issues or mobility disability, aerobic exercise with high intensity can be harmful.^{35,36}

Resistance exercise involves muscle contractions against external resistance, which can enhance muscle strength, muscle mass, and bone mineral density. Similar to aerobic exercise, it also improves insulin resistance and metabolic parameters. However, resistance exercise typically requires less body energy and is feasible for certain MASLD subjects with impaired cardiorespiratory function or those who are overweight or obese and unable to tolerate intense aerobic activity.^{35,36} A potential drawback of resistance training is the requirement for space and specific equipment, and it is less accessible and often more costly than aerobic exercise.

The benefits of aerobic and resistance exercise for subjects with MASLD have been reviewed comprehensively.⁴⁰⁻⁴⁴ Various exercise protocols of the two exercise patterns in the improvement of MASLD have been summarized in detail in a recent review article.¹² Given the high prevalence of cardiovascular issues and physical incapacity, especially in older populations with MASLD,^{45,46} it is essential to assess the risks of exercise. Exercise programs should be individualized based on underlying cardiorespiratory fitness as well as the presence of comorbidities to ensure safety and effectiveness.

Aerobic exercise improves hepatic steatosis in MASLD

Aerobic exercise is cost-effective and easily accessible. Hashida et al.¹² analyzed 24 aerobic exercise protocols from 18 studies (median age, 48 years; median BMI, 30.9 kg/m²). Most protocols involved exercising three times per week for 40 minutes per session over a 12-week period, and most adopted conventional MICT methods such as cycling. Overall, a decrease in intrahepatic fat was documented in 22 (91.7%) of the protocols. Nonetheless, aerobic exercise can cause fatigue and discomfort, potentially leading to lower adherence over time.

Resistance exercise improves hepatic steatosis in MASLD

Subjects with MASLD obtained similar benefits from resistance exercise in terms of body weight reduction and lower serum alanine aminotransferase levels in the review by Hashida et al.¹² Among seven studies, liver fat reduction was observed in 85.7% of the protocols (median age, 49 years; median BMI, 30.6 kg/m²).^{44,47-53} Mag-

netic resonance spectroscopy (MRS) was adopted for assessment of intrahepatic fat in three studies, disclosing intrahepatic fat reductions of 13%, 3%, and 25% from baseline, respectively.⁴⁷⁻⁴⁹ All protocols incorporated exercising three times per week for 45 minutes per session, with a median metabolic equivalent of 3.5, with the majority involving a 12-week period.

Based on these findings, 12-week resistance exercise can help improve hepatic steatosis. Performing three sets of 8–12 repetitions focusing on major muscle groups three times per week is generally recommended.

Notably, resistance exercise reduced hepatic steatosis without substantial weight loss and was less energy-intensive than aerobic exercise.^{47,51,54} These features can support the creation of individualized exercise programs based on personal physical condition including underlying cardiopulmonary function.

Comparison of aerobic exercise versus resistance exercise in the improvement of hepatic steatosis

To further compare the efficacy of aerobic exercise versus resistance exercise in the improvement of hepatic steatosis in subjects with MASLD, we searched the PubMed database for randomized trials investigating the improvement of hepatic steatosis with aerobic exercise versus resistance exercise from the year 2000. The following search terms were used: fatty liver, aerobic, resistance, and randomized controlled trials (RCTs). Finally, we identified seven trials, and the details are shown in Table 2.

MECHANISMS OF IMPROVEMENT

Definition and maintenance of metabolic flexibility

Metabolic flexibility refers to the body's inherent ability to use any available substrate as an energy source and is regulated by insulin and glucagon depending on its current needs.¹¹ In a resting state, the body transitions between glucose and lipids as main sources of energy. Postprandially, insulin stimulates the conversion of glucose into glycogen in the liver and aids in glucose absorption by the skeletal muscle. In periods of fasting, glucagon induces glucose synthesis and glycogenolysis in the liver and fat breakdown in adipose tissue, providing energy by releasing free fatty acids.

Regulated by the coordinated actions of insulin and glucagon,

this process enables the body to adapt its energy use according to eating or fasting conditions, helping maintain metabolic flexibility. Any disruption to this process, as seen in conditions such as MASLD, can disable the body's utilization and conversion between glucose and lipids.^{11,12,15} The impairment might induce lipid build-up in non-adipose tissues such as the liver, facilitating development of hepatic steatosis or leading to progression of MASLD.

Therefore, strategies to prevent or manage MASLD should prioritize preserving or restoring metabolic flexibility. Additional factors affecting metabolic flexibility include myokines, gut-liver axis, gut microbiome, mitochondria, peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) alpha, and peroxisome proliferator-activated receptor (PPAR) alpha.¹¹

Mechanisms of improvement through exercise

Briefly, aerobic exercise promotes insulin sensitivity and supports metabolic flexibility. Resistance exercise can improve metabolic flexibility through activation of AMPK, muscle fiber adaptation, and muscle-liver cross-talk.^{11,16}

Aerobic exercise

Aerobic exercise enhances insulin sensitivity. In adipose tissue, it facilitates lipolysis and beta-oxidation and increases acetyl-coenzyme A production, which increases adenosine triphosphate creation in the mitochondria.⁵⁵ Additionally, aerobic exercise upregulates uncoupling protein-1 and PPAR-gamma,⁵⁶ further enhancing lipolysis in adipose tissues.⁵⁷ Also, it has been found to reduce resistin levels and increase adiponectin levels in serum, which potentially benefits subjects with MASLD or metabolic dysfunction.⁵⁸⁻⁶⁰

Resistance exercise

Compared to aerobic exercise, the mechanisms accounting for the clinical benefits of resistance exercise are not fully clarified. Several studies have suggested that these benefits stem from muscle fiber type-specific adaptations. There are two types of muscle fibers: type I, which relies on slow oxidative metabolism, and type II, which depends on fast glycolytic metabolism. Resistance exercise primarily increases muscular strength and mass, particularly in stimulating hypertrophy in type II fibers rather than type I fibers. In addition,

Table 2. Characteristics of randomized clinical trials on subjects with MASLD: aerobic vs. resistance exercise

| Author (year) | Country/ethnicity | Subjects | Intervention | Assessment methodology | Case number | Intervention period | Parameters | Liver outcomes | Remark |
|---|-------------------|--------------------|--|--|-------------|---------------------|---|---|--------------|
| Slentz et al. (2011) ⁵³ | United States | Overweight | Aerobic exercise vs. resistance exercise | Computed tomography | 144 | 16 weeks | Liver fat, visceral fat, liver enzyme, and HOMA-IR | Both aerobic and resistance exercise reduced liver fat score; greater score reduction with aerobic training | |
| Lee et al. (2012) ⁴⁶ | United States | Obese adolescents | Aerobic exercise vs. resistance exercise vs. control | MR spectroscopy | 45 | 12 weeks | Liver fat, insulin sensitivity, and glucose | Both aerobic and resistance exercise trainings reduced liver fat score; resistance training improved insulin sensitivity | |
| Bacchi et al. (2013) ⁴⁹ | Italy | T2DM and MASLD | Aerobic exercise vs. resistance exercise | HMR spectroscopy | 31 | 16 weeks | Liver fat, insulin sensitivity, and subcutaneous adipose tissue | 10% reduction of hepatic fat in aerobic exercise; 12% reduction of hepatic fat in resistance exercise | |
| Shamsoddini et al. (2015) ⁵² | Iran | MASLD | Aerobic vs. resistance exercise vs. control | Ultrasonography | 30 | 8 weeks | Liver fat, liver enzymes, insulin sensitivity, and anthropometry | Equally effective for reducing liver fat | |
| Jia et al. (2018) ³⁴ | China | MASLD | Aerobic vs. resistance exercise vs. control | Ultrasonography, hepatic attenuation ratio | 474 | 24 weeks | Liver fat, liver enzyme, body composition, and NFS score | Effective for reducing liver fat in both exercise groups; higher reduction in the resistance group | Diet control |
| Lee et al. (2019) ³⁵ | United States | Overweight/obesity | Aerobic exercise vs. resistance exercise vs. combined exercise | MR spectroscopy | 118 | 24 weeks | Liver fat, insulin, and glucose | Liver fat was reduced in the aerobic exercise group (-0.6%) and combined (-0.6%) exercise group, but not in the resistance exercise group (-0.3%) | |
| Charatcharoenwitthaya et al. (2021) ³⁶ | Thailand | MASLD | Moderate intensity aerobic vs. resistance exercise | Transient elastography | 35 | 12 weeks | Liver fat, body composition, cardiorespiratory fitness, and glucose tolerance | Equally effective for reducing liver fat | Diet control |

MASLD, metabolic dysfunction-associated steatotic liver disease; HOMA-IR, homeostasis model assessment of insulin resistance; MR, magnetic resonance; T2DM, type 2 diabetes mellitus; HMR, Hongmeiren; NFS, NAFLD (nonalcoholic fatty liver disease) fibrosis score.

resistance training enhances the expression of the glucose transporter 4 (GLUT4) in type II fibers, contributing to a notable improvement in insulin sensitivity.⁶¹⁻⁶⁴ Overall, resistance exercise upregulates type II muscle fiber glycolysis, induces muscle changes, and ameliorates peripheral insulin resistance. Also, AMPK molecular signaling pathway can be activated during muscle contractions, which promotes the uptake of glucose by facilitating translocation of GLUT4 to the muscle cell surface. These mechanisms likely improve impaired metabolic flexibility and account for the clinical benefits of resistance exercise, including the decrease of intrahepatic fat in subjects with MASLD.

Hence, resistance exercise can help improve MASLD in part by facilitating communication between muscle and liver.^{65,66} One example of this mechanism is irisin, a myokine released by skeletal muscles. Irisin not only promotes thermogenesis and energy expenditure in subcutaneous adipocytes but also helps regulate lipid metabolism in the liver.⁶⁵ Recombinant irisin has been shown to inhibit the expression of liver lipogenesis regulators.⁶⁷ In obese mice, overexpression of irisin reduced liver fat content. Interestingly, the irisin serum levels were lower in MASLD subjects than healthy subjects.⁶⁸ Kim et al.⁶⁹ discovered that resistance exercise notably elevated irisin serum levels, a feature not observed in subjects performing aerobic exercise. These results indicate that resistance exercise impacts lipid metabolism and aids in reducing liver fat via the effect of irisin.⁶⁹

Overall, these mechanisms indicate that resistance exercise can help prevent or reduce liver fat accumulation in individuals with MASLD.

INTERESTING ISSUES REGARDING EXERCISE

HIIT vs. MICT aerobic exercise

There are two types of aerobic training protocols: MICT and HIIT (Table 3). MICT typically involves a steady intensity with a maximal oxygen uptake of 45% to 75%. In contrast, HIIT involves repeated cycles of high-intensity exercise or spring-type exercise interspersed with periods of recovery, achieving a higher maximal oxygen uptake of 80% to 90% over a shorter duration. HIIT has gained popularity as a time-saving exercise option.⁷⁰⁻⁷³ Due to the distinct characteristics of these exercise methods, it is uncertain which is more beneficial for improvement of aerobic capacity and other metabolic parameters.

In brief, both HIIT and MICT improve lactate clearance, increase aerobic capacity, correct metabolic derangement, and mitigate MASLD progression. Previous research disclosed that HIIT outperforms MICT in enhancing metabolic parameters, reducing visceral fat, and improving insulin sensitivity.⁷⁴⁻⁷⁶

Both HIIT and MICT increase clearance capacity of lactate

Lactate accumulation in the body influences aerobic exercise performance. Physiologically, glycolysis, which is responsible for the supply of body energy, involves break down of glucose to produce lactic acid and sequential conversion to lactate and protons.⁷⁷ Lactate clearance helps maintain acid-base balance and energy metabolism.⁷⁸ Normally, only a small amount of lactate exists in the body at rest, but the level increases significantly in a short time dur-

Table 3. Comparison of HIIT vs. MICT in subjects with MASLD⁷⁴⁻⁷⁶

| | HIIT | MICT | Remark |
|-------------------------------|--|---|----------------------------------|
| Metabolic parameters | Improved | Improved | HIIT was superior to MICT. |
| Reduction of intrahepatic fat | Yes | Yes | HIIT similar or superior to MICT |
| Mechanisms of improvement | Reduce anaerobic glycolysis Enhance lactate clearance Increase in muscle cell mitochondria and capillary density in muscle tissue | Similar to HIIT | |
| Features | Shorter time required Rapid improvement of cardiopulmonary fitness Higher post-exercise oxygen consumption Improved adherence in diseased cohorts | Traditional and well established Improve quality of life | |

HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; MASLD, metabolic dysfunction-associated steatotic liver disease.

ing intense exercise or in cases of circulatory diseases due to the insufficient oxygen supply.⁷⁹⁻⁸¹ When lactate accumulates in the body, blood and cellular pH decrease, impairing glycolysis and reducing exercise performance.

A recent study compared the effects of HIIT and MICT on lactate clearance, finding that both improved lactate clearance, but HIIT showed superior results.⁸²

Both HIIT and MICT improve aerobic capacity through reduction of anaerobic glycolysis. Briefly, HIIT and MICT benefit aerobic capacity by enhancing lactate clearance,⁷² with resultant reduction in the proportion of anaerobic glycolysis. These benefits are linked to changes in muscle cell mitochondria and capillary density in muscle tissue.⁸³⁻⁸⁵ In short, exercise increases the number of mitochondria and decreases glycolysis,⁸⁶ while also enhancing capillary density. These adaptations stimulate oxygen delivery to muscles and lower lactate production by decreasing anaerobic glycolysis. A recent systemic review revealed that the magnitude of change in the density of mitochondria, muscle capillarization, and maximal oxygen consumption (VO_{2max}) after exercise is mainly dependent on the level of baseline fitness, with individuals of lower fitness at baseline obtaining the greatest improvement.⁸⁷ Interestingly, the training load determined by both volume and intensity is a useful predictor of the changes in mitochondria number and VO_{2max} . Notably, the relative effects of HIIT versus MICT on mitochondrial number and capillary density remain unclear.⁸⁷⁻⁹⁰

Both HIIT and MICT improve cardiometabolic health

The effectiveness of HIIT and MICT in correcting metabolic derangement and improving clinical outcomes for individuals with metabolic syndrome was reviewed in a recent meta-analysis.⁹¹ Among five databases, 23 RCTs were collected, involving 1,374 participants (mean age, 46.2 to 67.0 years; 55% male). HIIT obtained significantly better improvements in all metabolic parameters compared to controls, with effects similar to those of MICT. Interestingly, low-volume HIIT protocols (< 15 minutes of high-intensity exercise) provided noninferior effects to higher-volume sessions in improving metabolic parameters. This review highlights the efficacy of HIIT as an alternative to traditional MICT for managing and improving cardiovascular and metabolic health in subjects with metabolic syndrome, even with low-volume protocols.

HIIT vs. MICT in the improvement of MASLD

The comparative effects of HIIT versus MICT on reducing intrahepatic fat in subjects with MASLD, the liver manifestation of metabolic syndrome, remain unclear. In animal models, although HIIT has been adopted to manage obesity and related comorbidities, its role in preventing or treating MASLD is not well established. A recent study investigated the effect of HIIT on preventing MASLD in C57BL/6J mice fed a high-fat diet. The study showed that HIIT helped maintain insulin sensitivity, prevent endoplasmic reticulum stress, and enhance beta-oxidation.⁹² These findings suggest that lifestyle modifications, including HIIT, can help treat obesity and prevent MASLD.

Another recent clinical trial explored the effects of combining HIIT with dietary restriction in a small, well-defined cohort.⁹³ The 10-month intervention examined the impact of the combination on liver and peripheral insulin sensitivity, liver histology (including steatosis, steatohepatitis, and fibrosis), anthropometrics, and plasma biochemical profiles in 16 participants. Compared to the standard of care (control group, $n = 8$), the combination of HIIT and energy restriction improved liver health, potentially by redistributing excess nutrients to skeletal muscle and reducing nutrient toxicity in the liver for subjects with advanced steatohepatitis related to metabolic dysfunction. Unfortunately, the impact of MICT versus HIIT on the improvement of MASLD or metabolic dysfunction-associated steatohepatitis were not investigated and compared in the study.

Our recent clinical trial provided comparative data on the effects of HIIT versus MICT on hepatic steatosis (submitted). Participants were divided into control ($n = 20$) and exercise ($n = 80$) groups, with the exercise group further randomized into MICT and HIIT subgroups. After 24 weeks of intervention, subjects received liver fat re-evaluation using magnetic resonance imaging-proton density fat fraction (PDFF), with the primary outcome defined as a > 10% decrease in PDFF. The results of the exercise group showed significant reductions in body weight (74.4 ± 14.0 kg vs. 73.3 ± 14.7 kg, $P = 0.004$), controlled attenuation parameter, PDFF, and MRS (290 ± 39 dB/m vs. 250 ± 40 dB/m, 7.03 ± 5.88 vs. 5.48 ± 5.12 , 9.43 ± 5.90 vs. 7.61 ± 5.25 , all $P < 0.001$), while the control group did not. Notably, there was no difference in body weight or hepatic steatosis reduction between the subjects performing MICT or HIIT. Our find-

ings consistently demonstrated exercise as an effective intervention for patients with MASLD. In particular, we first documented the lack of significant difference in treatment effects between MICT and HIIT exercise patterns.

In summary, MICT remains a valuable option for improvement of metabolic parameters in patients with metabolic syndrome and MASLD. Future research should focus on the integration of either MICT or HIIT into personalized fitness plans and exploring their benefits across various populations to refine and optimize exercise recommendations.

Maintenance and prediction of adherence

Adherence to lifestyle changes, including exercise, is crucial for patients with MASLD, as many struggle to maintain new exercise routines or dietary adjustments.⁹⁴ Improvements in weight loss and metabolic health are often difficult to sustain. Therefore, promoting and ensuring adherence is critical for patients with MASLD. In our recent exercise intervention trial, our data showed adherence to play a crucial role in intrahepatic fat reduction (submitted data). Specifically, completion of more than 75% of the entire exercise program was associated with a better treatment outcome in the reduction of liver fat. Supervised training is an effective strategy to enhance adherence regardless of exercise type.⁹⁵

Clinically, a reliable scoring or scale system is needed to assess adherence to exercise or diet interventions in subjects with MASLD. To address this issue, Zeng et al.⁹⁶ developed the Exercise and Diet Adherence Scale (EDAS) by identifying factors that affect exercise performance and diet adherence. The scale includes 33 items across six dimensions, which help categorize MASLD patients based on their level of adherence. A strong correlation between the scores and key lifestyle indicators was identified, enabling the classification of subjects by adherence level. In the future, this scale can be used to group patients according to EDAS scores, helping to develop individualized treatments aimed at improving adherence to various lifestyle interventions.⁹⁶

CONCLUSION

Exercise is an effective way to maintain body health and physical fitness and prevent or even treat metabolism-related systemic dis-

eases including MASLD. Any pattern of exercise can be helpful, either aerobic or resistance, HIIT or moderate intensity continuous training. Most importantly, adherence is the key toward successful outcomes and individualized strategies integrating other lifestyle modification and even novel pharmaceutical intervention are anticipated in the near future.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The work was supported by grants from the National Taiwan University Hospital; and the Ministry of Science and Technology (NSTC 112-2314-B-002-205-MY3, NSTC 113-2314-B-002-241), Executive Yuan, Taiwan.

AUTHOR CONTRIBUTIONS

Study concept and design: CL and CJL; drafting of the manuscript: CL and CJL; critical revision of the manuscript: CJL; obtained funding: CJL; administrative, technical, or material support: CJL; and study supervision: CJL.

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